the fact remains that, apart from pellagra and the encephalopathy of nicotinic acid deficiency, no other nicotinic-acid-responsive clinical psychopathology has been successfully—and definitively—identified.

In the absence of clinical evidence that schizophrenic patients benefit from nicotinic acid treatment, the recognition of biochemical heterogeneity within the schizophrenias becomes of crucial importance. We are attempting to determine if there are biochemically homogeneous subgroups within the schizophrenic population in which the administration of a methyl-acceptor substance (i.e., nicotinic acid) would be useful. These subgroups might be identified, for example, on the basis of the presence of bufotenine-like substances in the urine or demonstrated disturbances of transmethylation. To date, we have reached no consensus about which of a number of such criteria should form the basis for identifying homogeneous subpopulations in which the therapeutic efficacy of nicotinic acid might be tested more meaningfully.

In view of the absence of verified clinical or biochemical indicators of therapeutic responsiveness, the practical decision of whether to prescribe nicotinic acid must still be a clinical one.

The regulative norm must limit the chosen therapy to a favorable ratio between the possible adverse effects of treatment and the definite adverse effects of the untreated: One must not overlook the fact that schizophrenia is a severely debilitating disease; to withhold or categorically deny any treatment—either on the basis of empirical findings, medical thinking, or statistical probabilities—even if no scientific evidence has as yet been provided for its usefulness, may at this stage be contrary to the physician’s art. On the other hand, the prescription of a therapeutic regimen which has shown to be not the optimal treatment for the average schizophrenic patient before the optimal treatment has been tried may be contrary to the physician’s duty.

We must conclude that, in spite of all its limitations, pharmacotherapy with neuroleptics is the treatment of choice for schizophrenia today. Nicotinic acid should not be prescribed before neuroleptic treatment has been tried.

Whether a group of schizophrenic patients responsive to nicotinic acid can be identified through the application of presently available methods remains to be seen.

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megavitamin therapy—a reader’s view

To the Editor:

This is in regard to your invitation to share experiences with nicotinic acid and megavitamin treatment of schizophrenia.

I am a board-certified psychiatrist with a large private practice and large experience with drug therapy in schizophrenia. I have used nicotinic acid for at least 2 or 3 years, with other vitamins, in treatment of schizophrenia—sometimes routinely and sometimes only when the regular phenothiazine medication would not clear the symptoms completely. In about 80 percent of my cases there was an improvement when I introduced large doses of nicotinic acid with vitamin C, especially in areas of perception and ability to concentrate. It is interesting that patients themselves felt a great relief after started on this medication and urged me to continue.

Side effects were few and rare because I advised my patients to take a glass of cold milk or an antihistamine together with nicotinic acid and told them to always take it after meals. The maximum dosage I have used is 3 g./day of nicotinic acid and the same amount of vitamin C. I insist that, if taken correctly and according to the above mentioned advice, side effects are very rare. Even though there is no really logical and comprehensive explanation of the mode of action of megavitamin therapy, the fact remains that it is successful as an empirical treatment. In my case I use it only as an addition to psychotherapy and phenothiazines.

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Basic science has made possible many recent advances in our understanding of the biology of schizophrenia. In turn, techniques expressly developed for the study of schizophrenic processes have frequently been applied to a variety of other conditions—notably Parkinson's disease and depression. Nonetheless, the biological investigation of schizophrenia has had an uneven history. Several investigators have made discoveries which, at the time, were thought to be the biochemical cause of schizophrenia, but attempts to replicate and validate the evidence have too often failed. Thus, cycles of great expectations, questioning, disillusion, despair, and nihilism have been constantly recurring phenomena in schizophrenia research. Two interrelated aspects of this process are
especially troubling. Initially, the eminently human need for a simple, authoritative answer to a most difficult and frightening problem has often led us to embrace too readily, too impetuously, each biochemical solution to the schizophrenic conundrum. But, when the proffered solution is ultimately discarded (as frequently happens), a tendency exists for its former adherents, embittered at the loss of the hoped-for "total answer," to dismiss too hastily the very real contributions made to basic science by studies of the biology of schizophrenia.

Despite the confusingly complex history of this research area, no comprehensive, up-to-date review of the biology of schizophrenia has been published in the past several years. Hopefully, this gap will be filled by the article which follows. In an extensive review of many of the most relevant articles published over the past decade, Richard Wyatt, Benedict Termini, and John Davis highlight two major facets of the biological investigation of schizophrenia—studies of biochemistry and sleep. To put this important area into still finer perspective, Wyatt, Termini, and Davis' review is briefly commented upon by Arnold J. Friedhoff and Irwin Feinberg, discussants who have made significant contributions to the biological investigation of schizophrenia.

biochemical and sleep studies of schizophrenia: a review of the literature—1960–1970

part I. biochemical studies

Richard J. Wyatt, Benedict A. Termini, and John Davis

The etiology of schizophrenia remains undiscovered. Indeed, it is not yet clear whether the causative factors lie, as has often been assumed, in the biological realm or whether the widely accepted disease model of mental illness is, in fact, appropriate to the investigation of this complex disorder. All biochemical theories of schizophrenia are predicated on the belief that a qualitatively or quantitatively abnormal substance (such as a methylated amine or a protein) may play some role in producing schizophrenic episodes. Because existing biochemical "theories," at this preliminary stage of their development, might more accurately be termed research "leads" or "strategies," it is not necessarily an important scientific question whether these hypotheses are, in some absolute sense, true or false. A better question, it seems to us, is whether a given "lead" is worthy of further investigation or is an artifact.

The need to distinguish between artifact and reality has presented students of the biology of schizophrenia with a series of challenges perhaps unmatched in the history of science. That careful controls are essential in this research area was made abundantly clear by Kety (1959a and b) whose methodological criticisms of biochemical studies of schizophrenia are as relevant today as they were when his classic review was originally published. Since most investigators accept—at least in principle—the necessity for controls, we shall not repeat these criticisms for each individual study to be reviewed in these pages but, rather, emphasize here that results achieved in the absence of careful controls can be highly misleading. On a theoretical basis, the battle for controls has been won and need not be refought in this review. On a practical level, however, many studies fail to be well controlled.